HHS Public Access

Author manuscript

Ann Neurol. Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

Ann Neurol. 2015 September ; 78(3): 499–500. doi:10.1002/ana.24417.

Reply

Kwangsik Nho and **Andrew J. Saykin**

Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN 46234

We thank Dr. Yankner for his thoughtful comments regarding our report highlighting a protective association of a *REST* missense variant in mild cognitive impairment (MCI) based on a decreased rate of hippocampal atrophy on MRI.[1] We used whole exome sequencing to search for variants independent of the well-known *APOE* ε4 Alzheimer's disease (AD) risk factor by focusing on individuals with MCI with the common *APOE* ε3/ε3 genotype. In his Letter, Dr. Yankner noted the previously reported findings by Lu et al. that REST is lost in both MCI and AD and that REST represses genes that promote neuronal cell death and AD pathology in the aging human brain.[2] His letter also raised two questions regarding our findings with regard to subgroups: first, whether the *REST* variant protects against MCI or AD; and second, whether the *REST* variant protects against hippocampal atrophy in cognitively normal individuals. To address these important questions, we performed additional association analyses of the *REST* missense variant (rs3796529) and imaging phenotypes from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (N=1,566) used in our report. All non-Hispanic Caucasian participants regardless of *APOE* genotype were included. Lu et al. showed that REST was almost absent from the nucleus of cortical and hippocampal neurons (CA1, CA3 and CA4) in AD.[2] Therefore, we chose the CA1 subfield volume of the hippocampus as an imaging phenotype and computed the association of rs3796529 separately for each diagnostic group (Table). Regression analysis showed that rs3796529 was significantly associated with hippocampal CA1 volume in both MCI and AD participants, with minor allele carriers having larger CA1 volumes. In contrast, rs3796529 was not associated with the hippocampal CA1 volume in cognitively normal older adult controls (CN). Taken together, these reports[1, 2] provide complementary evidence implicating REST as a promising target for neuroprotective strategies for MCI and AD. Although our additional analyses did not support a role for *REST* in normal brain aging, this issue deserves further investigation given the findings by Lu et al.

References

1. Nho K, Kim S, Risacher SL, et al. Protective variant for hippocampal atrophy identified by whole exome sequencing. Annals of Neurology. 2015; 77:547–552. [PubMed: 25559091]
2. Lu T, Aron L, Zullo J, et al. REST and stress resistance in ageing and Alzheimer's disease. Nature. 2014; 507:448–454. [PubMed: 24670762]

Potential Conflicts of Interest

Nothing to report.

Hippocampal CA1 volume	CN		MCI		AD	
	β	*p*-value	β	*p*-value	β	*p*-value
Adjusting for *APOE* ε4 status	−4.948	0.1889	6.304	0.0247	10.63	0.0366
Without adjusting for *APOE* ε4 status	−4.992	0.1843	5.834	0.0380	10.42	0.0406